ATTORNEY DOCKET NO. 23016.0002US
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
	)	
Wynick, David	)	Art Unit: 1647
	)	
Application No. 09/230,463	)	Examiner: Gucker, S.
	)	
Filing Date: January 22, 1999	)	Confirmation No. 4323
	)	
For: "GALANIN"	)	

DECLARATION UNDER 37 C.F.R. § 1.132

1. I am Professor of Neuropharmacology in the Department of Pharmacology at University College, London, United Kingdom.

2. I have been associated with teaching and research in the subject of Neurosciences for 20 years and have published approximately 220 peer-reviewed papers and 20 review articles and chapters during this time. Examples of these publications together with details of my education are given in the short version of my *curriculum vitae* which is attached and shown as Exhibit A.

3. The work of my research group relates to the physiology and pharmacology of pain transmission and its modulation, with the aim of helping to improve the clinical management of pain. We study how neuronal activity in sensory pathways alters in different states and how this relates to pharmacological systems. Interest centers on the dorsal horn of the spinal cord where painful information can be modulated by both local and descending controls from the brain. The interactions between pain transmission systems and controlling influences, identification of the different transmitters in the incoming nerves, spinal cord neurones and long pathways descending from the brain, are features of this research. We also attempt to gauge the roles of ion channels, excitatory amino-acids, monoamines and neuropeptides, including galanin, in pain processing. The neural bases underlying prolonged pain are of great importance as are individual differences in pain and the ways in which emotional areas of the brain can influence transmission. The relative involvement of

peripheral nervous activity and the central nervous system in the generation of long lasting pain is another area of our research.

4. I am familiar with the work of David Wynick in the field of galanin and nerve regeneration.

5. I have reviewed the specification of US Patent Application Serial No. 09/230,463 ("the patent application"). I understand the technology described in the patent application. In particular, I have reviewed claim 18 of the patent application and its meaning is clear to me.

6. I have also reviewed the Office Action dated 9th August 2005 ("the Office Action") and the cited passage by Rudinger (taken from "Peptide Hormones", edited by J. A. Parsons & published by University Park Press in 1976). In relation to the objection raised by the Examiner in item 5 of the Office Action, I make the following comments:

7. The knowledge of the skilled person at the priority date of the patent application was far advanced from that represented by the disclosure of Rudinger. This textbook was published in 1976, twenty years before the priority date of the patent application and before the identification of galanin. During that time, the fields of biochemistry, neuroscience and pharmacology had changed a great deal.

8. A person of ordinary skill in the art would have been able, at the priority date (24th July 1996) of the patent application, to identify galanin agonists without undue experimentation. Indeed, the level of skill required would be that of a first year undergraduate in Pharmacology at a reasonable university. At the priority date at least six galanin agonists (in addition to the native full-length neuropeptide) had been identified. These include a number of chimeric ligands (where the N-terminal portion of galanin is fused to another peptide), including M15 [GAL-(1-13)-substance P-(5-11)amide], M35 [galanin-(1-13)-bradykinin-(2-9)-amide], M40 [galanin[1-13]-Pro-Pro-[Ala-Leu]2-Ala amide], and Gal(1-14)-[Abu8]SCY-I.

9. The following studies, using a variety of paradigms, demonstrated that each of the above ligands acts as a galanin agonist. M15 and M35 act as galanin agonists by causing contraction of jejunal muscle strips, and relaxing dispersed smooth muscle

cells from the rat small bowel (Gu *et al.* (1993) J. Pharmacol. Exp. Ther. **266** 912-918). Similarly, M15 acts as a galanin agonist by causing contraction of longitudinal muscle strips of the human colon in vitro (Katsoulis *et al.* (1996) Scand. J. Gastroenterol. **31** 446-451). Further, M15 and Gal(1-14)-[Abu8]SCY-I, acting as galanin agonists, both evoked concentration-dependent contractions of gastric smooth muscle strips (Korolkiewicz *et al.* (1996) Pharmacol. Res. **33** 361-365).

10. In insulin-producing RIN m5F cells, M15 and M35 both produce a biphasic response in calcium levels identical to galanin, demonstrating that both chimeric peptides act in this system as galanin agonists (Fridolf & Ahren (1993) Biochem. Biophys. Res. Commun. **191** 1224-1229; Kask *et al.* (1995) Regul. Pept. **59** 341-348). Similarly, a later study showed that M40 acts as a galanin agonist by stimulating glucose-induced insulin release from isolated mouse pancreatic islets (Bartfai *et al.* (1993) Proc. Natl. Acad. Sci. U.S.A. **90** 11287-11291). M40 also acts as a galanin agonist in the spinal cord (Xu *et al.* (1995) Br. J. Pharmacol. **116** 2076-2080). In addition, two N-terminally extended forms of galanin, galanin-(-7-29) and galanin-(-9-29) had also been shown to have agonistic properties on spinal flexor reflex excitability in decerebrate, spinalized, unanesthetized rats (Bedecs *et al.* (1994) Eur. J. Pharmacol. **259** 151-6).

11. Other assays to determine if a compound is a galanin agonist include the technique described by Botella *et al.* (1995) in the journal Gastroenterology **108** 3-11, in which they showed that galanin is an agonist at two types of receptor in intestinal smooth muscle where it contracts or relaxes the tissue.

12. Another way of identifying whether or not a compound was a galanin agonist would have been to examine its effects on the cholinergic control of vasculature tone in the anaesthetized rat, as reported by Barblivien *et al.* (1995) in the journal Neuroreport **6** 1849-1852. In this respect the agonist effect of galanin is to inhibit the vasodilatory cholinergic input.

13. It can been seen from the above studies that a variety of assays have been described which would allow a person of ordinary skill in the art to readily determine whether a compound is a galanin agonist and is, therefore, suitable for use in the method according to claim 18 of the patent application.

14. In summary, I believe that a person of ordinary skill in the art would have been able readily to identify galanin agonists at the priority date of the application and to identify compounds for use in the method according to claim 18 of the patent application.

15. In relation to the rejection of claim 18 for being obvious in light of Luo *et al.* ("Luo") and Zhang *et al.* ("Zhang"), I have also reviewed each of these documents. It seems that the Examiner considers that a compound which is effective in the amelioration of neuropathic pain that occurs as a result of nerve injury (as taught by Luo and then hypothesized by Zhang in primates) would have been obvious to the skilled person as having an effective use in the treatment of nerve damage by nerve regeneration.

16. There were a large number of drugs available for the treatment of chronic neuropathic pain which have no known effect on nerve regeneration. Examples include morphine and other opioids; aspirin; non-steroidal anti-inflammatory agents (NSAIDs); antidepressants such as Amitriptyline or Imipramine; and anti-epileptics such as Tegretol. Furthermore, there is common clinical experience that when drug treatment with these agents is halted, the pain returns, arguing against any restoration of the damaged nerve.

17. Studies have shown that:-

Morphine inhibits facial nerve regeneration (Sinatra, R. S. and Ford, D. H. (1979) Brain Res. **175** 315-25);

The antidepressant Imipramine has no effect on peripheral nerve regeneration in-vivo (De Medinaceli L. *et al.* (1986) Exp. Neurology **94** 788-90).

18. Therefore, in my view, there was nothing in the existing literature to make one of ordinary skill in the art think that chronic treatment of neuropathic pain (arising from nerve injury or damage), irrespective of the cause or the drug used, would promote nerve regeneration. Indeed, there was some data at the priority date of the current application to allow the opposite hypothesis to be proposed. Subsequent publications have supported this, for example Sabouni, F., *et al.* (Biochem. Biophys. Res. Commun. (1998) **248** 165-7) which reported that aspirin delays nerve outgrowth from cultured DRG neurons.

19. All of the existing data at the priority date of the current application was focused on treating pain and not on stimulating nerve regeneration. These two fundamental patho-physiological processes are very different and most, if not all, of the anti-pain drugs listed above act at the level of the spinal cord and brain to reduce electrical and chemical excitability and thus reduce pain transmission. In contrast, drugs that stimulate nerve regeneration do so at the level of the dorsal root ganglion (DRG) and/or the site of nerve injury.

20. For these reasons, it is my view that the skilled person would not have found it obvious to invent a method for the treatment of peripheral nerve damage (or of peripheral sensory neuropathy) in a subject comprising the step of administering a galanin agonist to the subject, wherein the peripheral nerve damage (or peripheral sensory neuropathy) is treated by nerve regeneration.

21. I further declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: October 31st 2005

Professor Anthony H. Dickenson